

PHARMACOTHERAPY OF NEONATES AND PREGNANT ANIMALS

Cory Langston, DVM, PhD, DACVCP

INTRODUCTION

The type and magnitude of change that occurs in physiology during pregnancy is often not appreciated by the veterinary practitioner. These changes can have a profound effect on drug disposition and hence patient response. Information on which drugs pose a danger to the embryo, fetus, and neonate can also be difficult to find. This presentation will address these issues from the standpoint of what risks the dam faces, what drugs are embryotoxic, teratogenic, or toxic to the fetus, and what special considerations need to be taken into account when treating very young animals.

THE DAM

Physiologic changes during pregnancy

During pregnancy there is a large increase in aldosterone production, 3-fold in women, that leads to increased sodium and water retention. As a result, blood volume increases 30-50%. In accordance with the Frank-Starling law cardiac output (CO) increases approximately 30-40%. This increased output meets the increased circulation demands of the pregnancy, however it leaves little cardiac reserve. Plasma protein concentrations are typically lower than normal during pregnancy, in part due to dilution from the increased blood volume and there may be a decreased binding affinity of drugs for those proteins. RBC counts decrease due to dilution. Depending on the species the anemia may be compensated for later in the pregnancy due to increased production by the bone marrow. In an iron deficiency, fetal hemoglobin will be maintained at the expense of maternal iron stores if necessary. With the increase in C.O. an increase in GFR also occurs and creatinine clearance may increase by as much as 50%. Though respiratory rate and depth may increase, the functional residual capacity of the lung decreases substantially, making the patient more prone to hypoxia, especially near term.

Changes in drug disposition affecting the dam

Because of the increased blood volume during pregnancy the volume of distribution (Vd) for many drugs is substantially increased. The Vd may also be increased due to lower plasma protein concentrations and associated binding, thereby allowing more drug to enter peripheral tissues. As a result, many pregnant patients require a larger dose of drug. For example the dose of gentamicin in the pregnant woman may be twice that required in the nonpregnant woman. The increase in Vd would also have the effect of decreasing drug clearance; however, the increase in GFR may counteract this. Rates of hepatic enzyme activity may also be increased (i.e. phenytoin metabolism in humans) or decreased (theophylline/caffeine). As such one can have confounding variables affecting drug disposition that can be difficult to predict. Therapeutic drug monitoring is particularly helpful in these situations.

Drug efficacy and toxicity in the dam

The primary risks of pharmacotherapy to the dam during pregnancy are more often a matter of decreased efficacy than toxicity. The large Vd and increased clearance mentioned above tend to create subtherapeutic concentrations. In general one should tend toward the higher end of a dosage range when treating the pregnant animal. There are however two unique antibiotic toxicities to be aware of. While tetracyclines are contraindicated in pregnancy due to the potential to stain the teeth of the fetus, a lesser-known reason to avoid them is that they have been linked to fulminating hepatitis in the bitch and women. Also, erythromycin estolate may cause a cholestatic hepatotoxicity by an unknown mechanism.

THE FETUS

The blood-placenta barrier

You probably remember memorizing in veterinary school the types of placenta that the different species have. While those differences may have anatomical and immune implications, they don't have much effect on the passage of drugs. In fact, the truth is that the blood-placenta barrier is not much of a barrier at all. For the most part anything the mother has in her central circulation will be passed to the fetus, albeit at different concentrations. There are of course exceptions. Heparin is considered the anticoagulant of choice in the pregnant animal as its large size and high degree of ionization prevent its passage across the placenta, but this is quite unusual. A rule-of-thumb for predicting on which side of the placenta a drug may concentrate is based on pH partitioning. Since the pH of the fetus is slightly acidic relative to the dam, weak bases

accumulate on the fetal side while weak acids stay predominantly on the maternal side. The bottom line again however is that most drugs reach the fetus to some degree.

Stages of fetal development and associated susceptibility to teratogens

Understandably a great deal of the concern in treating a pregnant animal is directed at avoiding teratogens. The usefulness of teratogenic drug evaluations is somewhat limited depending on a variety of variables including dose, route of administration, species tested and the associated ability of the fetus to metabolize a drug (typically limited in domestic animals unlike in the human fetus), and the timing of drug administration. While all variables play a role, it is generally conceded that time of administration relative to development is much more important than the dose administered.

Fetal development is typically divided into four stages: blastogenesis, embryogenesis, metamorphosis, and fetal growth. Actually early in gestation during predifferentiation the blastocyst is relatively resistant to the induction of congenital malformations though exposure during this time may interfere with implantation and terminate pregnancy. It is during differentiation within the embryonic stage and organogenesis during metamorphosis that most abnormalities occur. From the end of metamorphosis until birth, when most growth occurs, the fetus becomes progressively less susceptible to teratogenic effects. Table 1 shows the stages of gestation for the major species.

Table 1: Stages of gestation for common species¹

Species	Implantation occurs (days)	End embryonic period (days)	End metamorphosis (days)	Birth (days)
dog	14-21	20	30	63-68
cat	13-17	18	22	64-66
horse	25-70	26	35	329-345
cow	30-36	30	45	278-290
swine	20-24	20	35	112-116
man	7-8	36	60	267

Nonteratogenic adverse drug effects on the fetus

Congenital malformations are not the only risks to the fetus associated with drug administration to the dam. Table 2 lists drugs felt to be safe during pregnancy while Table 3 lists drugs thought to be hazardous.

**Table 2: Drugs considered (relatively) safe during pregnancy^{2,3,4,5}
(Always use for shortest duration of treatment possible.)**

Analgesics (short-term)	Antiemetics	Bronchodilators
codeine	promethazine (Phenegan)	theophylline
morphine	prochlorperazine (Compazine)	terbutaline
Anti-inflammatories	metoclopramide (Reglan)	beta-adrenergic agonists (albuterol, isoproterenol, metaproterenol)
glucocorticoids - risky; avoid in 1st trimester; use pred instead of dex	Antihistamines*	Diuretics
Antimicrobials	diphenhydramine (Benadryl)	furosemide (Lasix)
penicillins	chlorpheniramine (Chlortrimeton)	mannitol
cephalosporins (cefactor, cephalixin and cephradine questionable)	Antiarrhythmics	Gastrointestinal Drugs
sulfonamides (except in 3rd trimester)	atenolol (Tenormin)	ranitidine (Zantac)
sulfamethoxazole/trimethoprim (controversial in 1st trimester)	lidocaine	famotadine (Pepcid)
erythromycin (except erythromycin estolate)	Anthelmintics	sucralfate (Carafate)
clindamycin	fenbendazole	Local anesthetics
metronidazole (some conflicting evidence)	ivermectin	lidocaine
Anticoagulants	pyrantel	
heparin	Antidepressants	
	amitriptyline (Elavil)	
	fluoxetine (Prozac)	

Table 3: Drugs to avoid during pregnancy ^{2,3,4,5}

Drug	UNTOWARD EFFECTS
ACE inhibitors	Renal failure, oligohydramnios, limb and craniofacial deformities
aminoglycosides	Ototoxicity when taken in first trimester
benzodiazepines	Teratogen. Possible fetal syndrome similar to fetal alcohol syndrome in humans
cefactor, cephalixin, cephadrine	Associated with possible teratogenic effects ¹⁵²
cimetidine	Possible antiandrogenic effects in fetus
DMSO	Teratogen
griseofulvin	Teratogen
iodines	Fetal goiter
meclizine	Teratogen
NSAIDS	Increases bleeding risk at delivery, decreased uterine contractility, chronic use may lead to oligohydramnios or neonatal pulmonary hypertension, best to avoid use
phenylpropanolamine	Increased risk of birth defects
pseudoephedrine	Increased risk of gastroschisis
fluoroquinolones	Bind to cartilage and bone, consequences are debated
tetracyclines	Discolor teeth
thiazides	Fetal death and thrombocytopenia

THE NEONATE

Physiological difference in neonates versus adults

The adage that a puppy is not just a small dog is definitely true when it comes to drug therapy and the same can be said for other species. Most of our domestic animals receive their passive immunity through absorption of colostrum at first nursings. This first 24 hours is a time when the intestine will also absorb a variety of oral drugs, such as aminoglycosides, that normally would not be absorbed in the adult.

Particular attention must be paid to orally administered drugs in neonatal ruminants. Within the first week of life most drugs that are absorbed orally in small animals can be used effectively in calves. Somewhere between week three and six however rumen activity increases and the calf must be viewed as an adult ruminant from the standpoint of oral drug administration.

Neonates have a much greater percentage of body water and less fat than adults. The total body water of cattle shifts from 74% of body weight in newborn calves to 58% in adult cattle, with the decrease primarily associated with the extracellular fluid compartment. Hypoproteinemia, primarily due to low albumin, also allows greater peripheral distribution of drug. Neonatal hypoalbumenemia, most evident in the piglet, increases to adult values within 2 to 3 week. For both reasons neonates typically have a greater volume of distribution than adults and may require a larger initial dose than adults. With age, fat content increases in calves from 3% at birth to 18% as an adult. This decreased fat content and lower protein binding in the neonate, along with a more porous blood brain barrier, accounts for the greater sensitivity to barbiturates seen in neonates. Typically a barbiturate should be reduced about 25% of the usual effective dose at one month of age or younger.

Liver and renal function differences account for most of the differences in neonatal physiology. Unlike the human being where even the fetus has substantial hepatic metabolic capability, the domestic animals are born with little liver metabolic capacity. As such, drugs that are eliminated by metabolic processes will have prolonged half-lives in neonates. The horse is the exception among species in this regard. Though also born naive, the foal rapidly develops drug metabolic capability over the first 1 to 3 days of its life such that it functions as an adult after 3 days of age.⁶ Other species typically require 4 to 5 weeks to reach drug metabolic maturity.

There are also significant species differences relative to renal excretory ability in neonates. Calves, foals, and pigs have considerable excretory renal function at birth while puppies and kittens require about 2 to 3 weeks to approach adult values.

Treatment guidelines in the neonate

Generally one should avoid in neonates drugs that require hepatic metabolism for either activation or removal. When possible, use renally excreted drugs with a high safety margin. The clinician must also be aware of what drugs cross into the milk if treating a nursing animal.

If general anesthesia is required, gas inductions are preferred. When barbiturates are used the usual dose should be reduced 25% but prolonged recoveries should be expected. Opioids are useful adjunct in anesthesia or pain control as they can be reversed. Beta-lactams are typically preferred antibiotics.

REFERENCES

- 1 Schardein, JL. Principles of testing teratogenic effects. In: James L. Schardein, ed. *Drugs as teratogens*. : CRC Press, 1976, Cleveland, p9-34.
- 2 Niebyl JR. Drug use in pregnancy and lactation. In: Pearlman MD, Tintinalli JE, eds. *Emergency Care of the Woman*. New York: McGraw Hill; 1998: 165-178.
- 3 Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation. 4th Ed*. Baltimore: Williams & Wilkins, 1994;148-149.
- 4 Papich MG, Davis LE. Drug therapy during pregnancy and in the neonate. *Vet Clin North Am Small Anim Pract*. 1986 May;16(3):525-38.
- 5 Hals G, Crump, T. The Pregnant Patient: Guidelines for Management of Common Life-Threatening Medical Disorders in the Emergency Department. *Emergency Medicine Reports*; March 13, 2000, <http://www.healthcarecontent.com/reports.html>.
- 6 Short CR. Drug disposition in neonatal animals. *J Am Vet Med Assoc*. 1984 May 1;184(9):1161-2.

Keywords

pregnancy, neonate, age effect, teratogen, pharmacokinetics, gestation, hepatic metabolism, renal excretion, species differences